Severe gastrointestinal hemorrhage due to metastatic renal cell carcinoma to the pancreas successfully controlled by transarterial embolization and adjuvant administration of Sunitinib Malate

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SEVERE GASTROINTESTINAL HEMORRHAGE DUE TO METASTATIC RENAL CELL CARCINOMA TO THE PANCREAS SUCCESSFULLY CONTROLLED BY TRANSARTERIAL EMBOLIZATION AND ADJUVANT ADMINISTRATION OF SUNITINIB MALATE

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Metastatic renal cell carcinoma to the pancreas rarely causes massive gastrointestinal hemorrhage. Management of patients who cannot undergo pancreaticoduodenectomy is difficult. Here, we report a case of severe gastrointestinal hemorrhage that was successfully controlled by combination therapy of transarterial embolization and Sunitinib Malate administration. Transarterial embolization was effective in controlling the acute phase of hemorrhage, and Sunitinib Malate effectively achieved long term control. We propose that such combination therapy is useful for hemorrhagic events due to renal cell carcinoma.

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Key words : Renal cell carcinoma, Pancreas, Metastasis, Embolization, Sunitinib malate

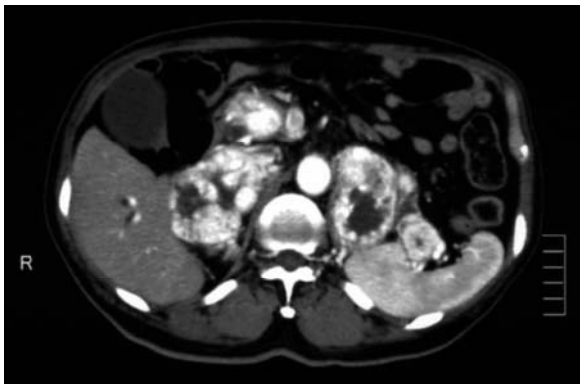
INTRODUCTION

The pancreas is a rare site of metastatic renal cell carcinoma. Pancreaticoduodenectomy is the definitive treatment applied to patients with a solitary metastasis[1]. However, management of patients with concomitant metastases in other sites or those who are not candidates for aggressive surgery remains controversial. Here, we report a case of severe gastrointestinal hemorrhage and obstructive jaundice due to metastatic renal cell carcinoma to the pancreas that was successfully controlled with transarterial embolization (TAE) and adjuvant administration of Sunitinib Malate.

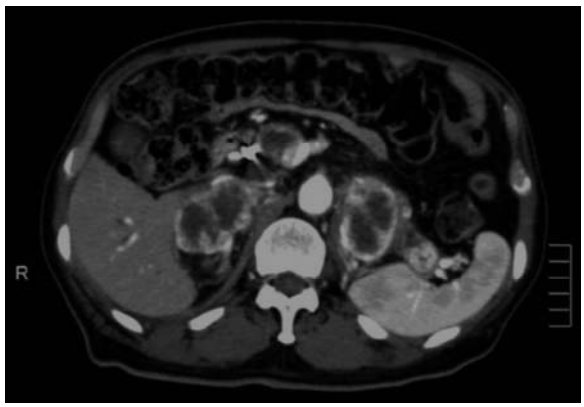
CASE REPORT

A 73-year-old man presented with melena. He had undergone left radical nephrectomy for renal cell carcinoma 18 years ago. Pathological result at that time was renal cell carcinoma, clear cell type, G1, pT3b, N0, M0 (1987 TNM classification). Thirteen years later, multiple lung nodules were discovered. Since the nodules slowly grew in size, the patient was diagnosed with pulmonary metastatic renal cell carcinoma, and interferon-α therapy was started. Size of nodules decreased temporarily, and nodules almost stabilized thereafter. Abdominal computed tomography (CT) performed 1 year prior to presentation showed no sign of metastasis in other visceral organs.

At presentation, the patient was in a pre-shock state due to melena. On physical examination, icterus was noted. CT scan (Fig. 1) revealed hypervascular tumors with very strong contrast enhancement in bilateral



(A)



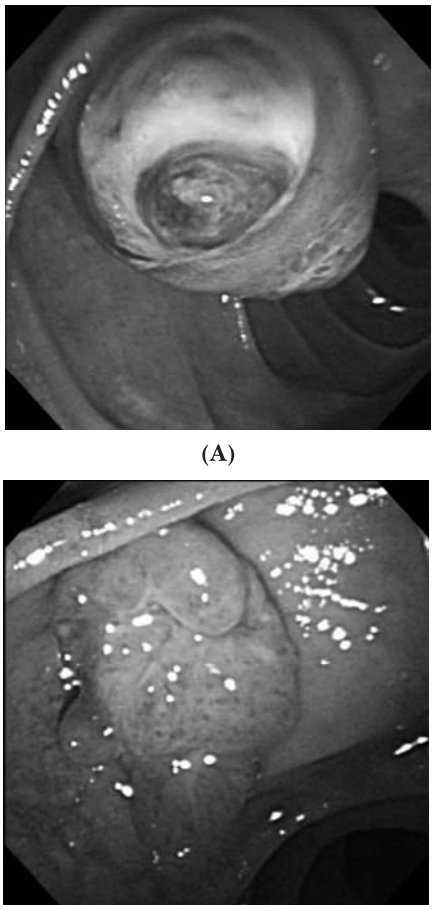
(B)

Fig. 1. CT before treatment (A) compared to CT 3 months after Sunitinib Malate administration (B). Sizes of tumors have decreased, and tumors necrotized after treatment.

adrenal glands and the pancreatic head, compatible with metastatic renal cell carcinoma. Common hepatic and intrahepatic bile ducts were dilated due to obstruction by the pancreatic tumor. Adrenal and pancreatic hormone levels were not elevated. Gastrointestinal fiberscopy (GIF) revealed a hypervascular tumor at the duodenal papilla penetrating the duodenal mucosa. Due to high risks of further bleeding, biopsy was not performed. Radiologic findings and negative hormone examinations resulted in diagnosis of metastatic renal cell carcinoma to bilateral adrenal glands and the pancreas. Since there was no active arterial bleeding site by GIF, a hemostatic procedure was not performed, and the patient was conservatively followed with transfusion. Melena continued, and the patient necessitated transfusion almost every other day to maintain his hemoglobin level. Two weeks after admission, the patient entered a pre-shock state once again with severe melena. GIF revealed a large pulsating vessel on the surface of the tumor impending to rupture. Size of the tumor penetrating the duodenal mucosa had almost doubled in the 2 weeks, and bleeding couldn't be controlled endoscopically. After the risks of duodenal perforation and pancreatitis were explained, the patient agreed to TAE.

An angiogram revealed a hypervascular tumor compatible with metastatic renal cell carcinoma at the pancreatic head. The tumor was receiving blood supply from both anterior and posterior pancreaticoduodenal arterial arcades. No extravasation of contrast was observed. Since preservation of either of the arcades was not possible, embolization was performed as selectively as possible to minimize the risk of ischemic complications. All embolizations were performed with coils to minimize accidental embolizations of small collateral arteries feeding the duodenum and the pancreas. Angiograms of the celiac trunk and the superior mesenteric artery after embolization showed that all feeding arteries of the tumor had been successfully embolized. Melena stopped right after embolization, and the patient's hemoglobin level could be maintained without further transfusion. The patient didn't complain of any abdominal pain after embolization, and icterus disappeared a few days later. Laboratory data 4 days later showed increased hemoglobin, and decreased bilirubin and alkaline phosphatase levels. Amylase was not elevated.

One week later, GIF showed that although the size of the tumor hadn't changed, the pulsating vessel on the surface of the tumor had disappeared, and the tumor didn't bleed with manipulation with an endoscope. There was no sign of ischemic damage to the duodenum. CT obtained 2 weeks later showed significantly decreased contrast uptake by the tumor. However, minor melena recurred 3 weeks after embolization. It was suspected that new vascular supply developed to the tumor. To control vascular growth, 50 mg Sunitinib Malate was orally administered daily. Since the Ministry of Health in Japan had not approved Sunitinib Malate yet, the patient personally imported the agent. Institutional review board approval and written informed consent was obtained before its administration. CT at the end of the first 6-week cycle showed that most of the pancreatic and adrenal tumors had necrotized. Size of the tumor had drastically decreased by GIF (Fig. 2). The patient was entirely free of any melena after 1 week of Sunitinib Malate administration. Due to Grade 3 thrombocytopenia, the daily dose of Sunitinib Malate was reduced to 37.5mg, and it was safely continued without further major side effects for 8 months. No re-growth of tumors was observed by CT or GIF during the period and no gastrointestinal hemorrhage recurred. However, the patient refused to continue the drug due to its high price after 8 months and severe gastrointestinal hemorrhage recurred soon after its discontinuation. Both pancreatic and adrenal tumors showed rapid re-growth. The patient denied resuming Sunitinib Malate administration and he is conservatively followed with multiple transfusions, hemostatic procedures by GIF, and nil per os status.



(A)

(B)

Fig. 2. GIF before treatment (A) compared to GIF 2 weeks after Sunitinib Malate administration (B). The bulging tumor drastically decreased in size after Sunitinib Malate administration.

DISCUSSION

Metastastatic renal cell carcinoma to the pancreas is rare, comprising about 2% of all renal cell carcinoma cases. About half of these cases involve solitary metastases[1]. While pancreaticoduodenectomy is the treatment of choice for solitary diseases, management of such cases with concomitant metastases in other sites remains controversial. Effectiveness of TAE for unresectable primary diseases or metastatic diseases in renal cell carcinoma patients has been established[2]. However, there is no report on the effectiveness of TAE for metastatic renal cell carcinoma to the pancreas, and only 2 reports exist on TAE for gastrointestinal bleeding due to duodenal invasion of renal cell carcinoma[3,4]. This is probably because TAE is avoided in such body region due to risks of ischemic complications such as pancreatitis and duodenal ulcers. However, in cases of uncontrollable gastrointestinal bleeding due to other causes[5,6] or in cases of pancreaticoduodenal aneurysms[7], TAE is often performed to gain vascular control.

In order to avoid ischemic complications following TAE, we emphasized 2 factors. First, embolization should be performed as selectively as possible. Secondly, embolization should be performed with larger size particles such as coils. Some investigators reported that smaller size particles such as gelfoam powder could inadvertently embolize small collateral arteries to normal tissues, causing ischemic damage[6,8,9].

Duration of effects of TAE is limited in metastatic renal cell carcinomas because the tumor recovers its blood supply from adjacent vessels. Sunitinib Malate is a multitargeted inhibitor of vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) that has anti-tumor activities against metastatic renal cell carcinoma. Inactivation of VEGFR and PDGFR reduces angiogenesis and tumor growth[10]. In our case, we suggest that Sunitinib Malate prevented the development of new vascular supply to the tumor, thereby preventing further gastrointestinal hemorrhage. We speculate that Sunitinib Malate is a potential agent in managing hemorrhagic events due to renal cell carcinoma.

TAE was very effective in controlling the acute phase of severe gastrointestinal hemorrhage when performed by an experienced radiologist, and the use of Sunitinib Malate successfully resulted in long term control of hemorrhage. We conclude that the combined use of TAE and Sunitinib Malate may be very effective both in acute and chronic phases of hemorrhagic events due to renal cell carcinoma.

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和文抄録

血管塞栓術および Sunitinib Malate 投与で止血し得た腎癌膵頭部転移に伴う難治性消化管出血の 1 例

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腎癌の膵転移は稀に大量の消化管出血をきたすことがある．これらの患者のうち，手術適応とならない患者では止血に難渋する．われわれは，動脈塞栓術およびスニチニブの併用によって長期にわたり止血しえた腎癌膵頭部転移に伴う難治性消化管出血の 1 例を経験したので報告する．血管塞栓術は出血の急性期において有効であった．また，スニチニブによって長期間の止血が可能であった．腎癌による出血性の症状に対してはこのような併用療法は非常に有効であると考えられた．

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